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Rh-Catalyzed Stereospecific Synthesis of Allenes from Propargylic Benzoates and Arylboronic Acids

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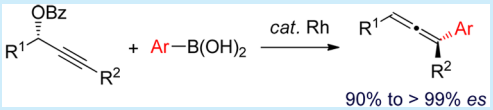
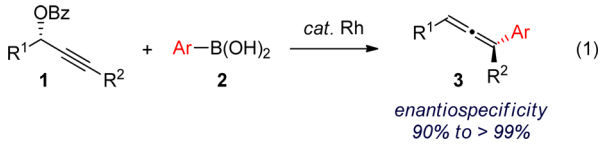
Supporting Information

ABSTRACT: An enantiospecific approach to the synthesis of optically active, trisubstituted allenes from chiral propargylic benzoates and arylboronic acids has been developed. The transformation is catalyzed by a Rh−(P,olefin) complex formed *in situ* from [{Rh(cod)Cl}$_2$] and a readily available phosphoramidite ligand. The method furnishes an assortment of diverse allenes in high yields and excellent enantiospecificity under mild conditions.



Allenes are an important class of compounds due to their unique reactivity and their use as building blocks in complex molecule synthesis.[1] The transition-metal-catalyzed S_N2' reaction between propargyl alcohol derivatives and organometallic reagents constitutes one of the most important approaches for the preparation of optically active allenes.[2] Herein, we disclose a preparation of enantioenriched allenes from chiral propargylic benzoates and arylboronic acids. The reaction employs a Rh-catalyst formed in situ from a simple, achiral phosphoramidite ligand and commercially available [{Rh(cod)Cl}$_2$]. This method allows access to chiral, trisubstituted allenes in high enantiomeric excess from the corresponding propargylic alcohols (eq 1). As such, the Rh-



(1)

catalyzed synthesis of chiral allenes from widely available boronic acids is complementary to related, previously reported Cu- and Pd-catalyzed reactions.[3] Furthermore, to the best of our knowledge, a transition-metal-catalyzed, enantiospecific synthesis of chiral, trisubstituted allenes from propargyl alcohol derivatives and arylboronic acids has not been reported.

The traditional approaches to allenes from propargyl electrophiles prescribe the use of stoichiometric amounts of reactive organometallic reagents as coupling partners, derived from In(III), Zn(II), Mg(II), and Cu(I). More recently, alkyl-, vinyl-, and arylboron reagents have been used in the preparation of chiral allenes from enantioenriched propargylic alcohol derivatives under Pd- or Cu-catalysis.[3] The sole example involving Rh-catalysis employs alkynyl epoxides as electrophiles and arylboronic acids, in a reaction displaying high regio- and stereoselectivity to give allenes.[4,5] However, the requisite starting materials, namely optically active alkynyl epoxides, are not readily accessible, requiring a multistep sequence of reactions for their synthesis. Enantioenriched propargylic alcohols on the contrary may be readily accessible from the asymmetric addition of terminal alkynes to aldehydes[6] or the reduction of α,β-alkynyl ketones by the methods described by Corey, Noyori, or Midland.[7]

Our investigations commenced by studying the Rh-catalyzed reaction between propargylic carbonates and phenylboronic acid (**2a**) as test substrates. In the presence of [{Rh(cod)Cl}$_2$], ligand **4** (1:1 ligand/Rh), and Cs_2CO_3 in 1,4-dioxane/water, the reagents were observed to undergo reaction to furnish the corresponding allene. However, under these conditions, no chirality transfer was observed, leading to product formation as a racemate. After extensive experimentation, we observed that variation of the solvent, ligand (e.g., **4**−**10**), ligand-to-metal ratio, and base had a significant impact on the yield and enantiospecificity of the process. Propargylic benzoates were found to give comparable results as carbonates (see Supporting Information for an example) while 4-NO_2-benzoates gave the products with lower selectivity. Accordingly, when the reaction between propargylic benzoate **1a** (96% *ee*) and phenylboronic acid (**2a**) was conducted in 1,2-dichloroethane as solvent with 2:1 **4**/Rh(I) and K_3PO_4 as base, full conversion to adduct **3a** in 98% *es* was observed (Table 1, entry 1). Following a screening of a number of other ligands (**5**−**10**), phosphine-olefin phosphoramidite **4** was identified as the optimal ligand (see Supporting Information for details).[8]

With the optimal reaction conditions identified, the scope of the method was examined (Scheme 1). Propargylic benzoates (*ee* ≥ 96%) **1a**−**j** were prepared by the asymmetric addition of terminal alkynes to aldehydes and subsequent benzoylation.[6a] Benzoate **1k** was accessed through CBS-reduction of the corresponding α,β-ynone.[7d] Reaction of these benzoates with various arylboronic acids **2** gave allenes **3** in good to excellent yields, and the observed selectivities were high (≥90% *es*) in all cases. The propargylic electrophiles can be substituted with a protected amine (**3f**−**3h**), ester (**3a**−**3e**), or alkyl bromide (**3k**). Electron-rich (**3c**, **3d**, **3h**) and electron-poor (**3f**, **3i**, **3j**) arylboronic acids may serve as coupling partners. *Ortho*-

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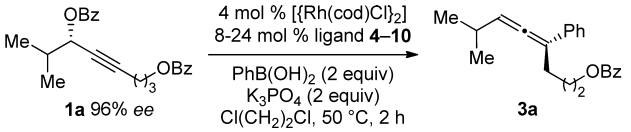
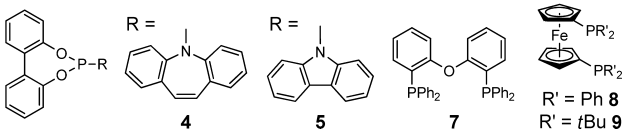
Table 1. Selected Ligand Screening Studies





entry	ligand	conversion (%)[a]	*es* (%)[b]
1	**4**	>95	98
2	**5**	46	98
3	$(BnO)_2PN(iPr)_2$ (**6**)	<5	n.d.[c]
4	**7**	>95	89
5	DPPF (**8**)	>95	91
6	**9**	>95	94
7	$P(OMe)_3$ (**10**)	61	83

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. [c]Not determined.

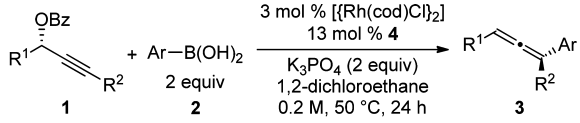
substitution of the boronic acid was well tolerated (**3b**, **3e**). Although most substrates gave full conversion and good to excellent yields using readily available [{Rh(cod)Cl}$_2$] under the conditions described above, we have found that the addition of water generally led to an increase of the reaction rate while the selectivity was slightly lowered. For example, full conversion (96% yield) and 95% *es* were observed in the synthesis of **3g** when 10 equiv of water were added to the reaction mixture. In the absence of added water, an allene adduct was isolated in 79% yield and 99% *es*. We also noted that the use of [{Rh(cod)OH}$_2$] resulted in higher conversions in certain cases.

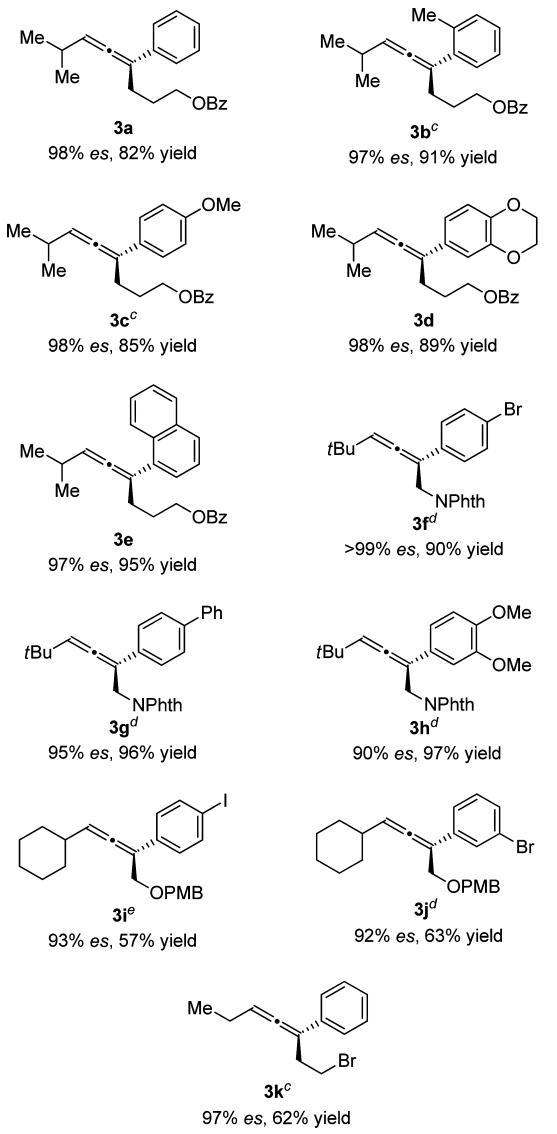
In general, the substrates can be substituted with linear, branched secondary or tertiary alkyl groups (R^1) in α-position to the propargylic benzoate. The reaction is slower with increasing size of the substituent on the alkyne distal to the benzoate (R^2). The starting materials were cleanly recovered for substrates with Me_3Si-substituted alkynes (R^2). As a limitation, strongly electron-poor arylboronic acids as well as vinyl- and alkylboronic acids are not suitable coupling partners at the current level of development. Preliminary experiments revealed that the use of terminal alkynes in the reaction gave a complex mixture of products, from which none could be identified as being allenes.[9,10]

The structures of three allene products (**3f**–**3h**) were confirmed by X-ray crystallographic analysis, and the absolute configuration for **3f** was established accordingly.[11] On the basis of this configurational assignment, some insight can be gained and a mechanism can be proposed. Hence, the reaction likely proceeds through regioselective arylrhodation of the alkyne to give an organorhodium intermediate (Scheme 2: **12** + **1** → **13**) followed by a selective *syn*-elimination to yield the observed allene.[4a,5a,12] An alternative mechanism proceeding through an allenyl-Rh intermediate cannot be excluded.[3a–c] Interestingly, no products from direct S_N2 substitution were observed.

In conclusion, we have disclosed the first example of a Rh-catalyzed, stereoselective synthesis of allenes from chiral propargylic alcohol derivatives and arylboronic acids. This method furnishes structurally diverse trisubstituted allenes in good yields and with high stereoselectivity (≥90% *es*). The chiral propargylic alcohol derivatives employed are readily accessible through enantioselective addition of alkynes to aliphatic aldehydes or asymmetric ketone reductions. Thus, the method allows the synthesis of enantioenriched allenes in a convergent and stereoselective manner from simple precursors under mild conditions and without the use of sensitive organometallic reagents.

Scheme 1. Scope of the Rh-Catalyzed Synthesis of Trisubstituted Allenes[a,b]





[a]Yields refer to isolated products after purification by chromatography on silica gel. [b]Enantiomeric excesses were determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. [c]Reaction conducted at 40 °C for 12 h. [d]10 equiv of H_2O were added. [e]10 equiv of H_2O were added, and [{Rh(cod)OH}$_2$] (3 mol %) was used.

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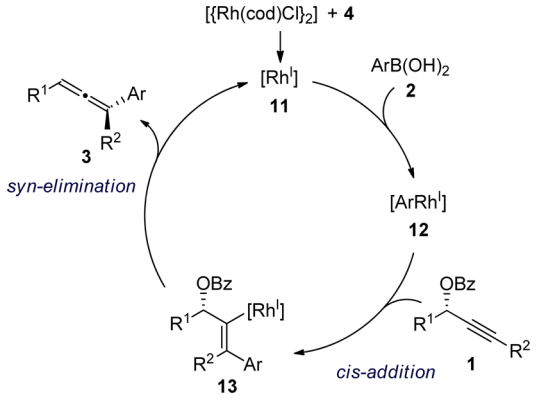
Scheme 2. Mechanistic Proposal Accounting for the Observed Absolute Configuration through *cis*-Addition and *syn*-Elimination[5a]



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00793.

Experimental procedures, characterization, and NMR spectra for obtained compounds (PDF)
X-ray data for compound **3f** (CIF)
X-ray data for compound **3h** (CIF)
X-ray data for compound **3g** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1437268 (**3f**), 1446561 (**3g**), and 1437269 (**3h**) contain the supplementary crystallographic data for this publication. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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